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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
MARVICH, MARIA	

ART UNIT	PAPER NUMBER
1633	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/806,346	URTHALER ET AL.	
	Examiner	Art Unit	
	MARIA B. MARVICH	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *3-9,11-20,23,24 and 40-44* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *3-9,11-20,23,24 and 40-44* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *23 March 2004* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

This office action is in response to an amendment filed 9/2/08. Claims 3-9, 11-20, 23, 24 and 40-44 are under examination in this application.

Claim Objections

Claims 40 and 4 are objected to because of the following informalities: Claim 40 in line 2 should be amended for clarity to recite --device, the method comprising--.

The claim construction throughout steps a) through d) suffers from a lack of clarity and omission of several requirements. First, the claim is drawn to use of a device, which appears to be a lysis reactor, a neutralizing reactor and a clarification reactor in fluid connection to one another wherein the fluid connection is tubing that introduces the solution from one reactor to the next. However, after mention of the device in the preamble no further mention is made. Secondly, in step a) the recitation that the cell suspension is a formation broth containing the cultivated cells lacks recitation of where the fermentation broth originates, are the cells cultivated in the broth or transferred into it? Thirdly, mention is made to introducing into the lysis reactor of a lysed cell solution "at a defined ratio of flow rates". However, there is no mention of what is driving the flow rate. According to the specification the result of pumps or pressurized gas that transports the solutions from one reactor to the next. Fourth, the steps of "c) neutralizing in a neutralization reactor", "d) separating in a clarification reactor" suggests the hand of man whereas each is a consequence of a reaction that occurs in the perspective reactors. The construction and clarity of claim 40 would thus be improved by the following amendments. First, by reciting in the preamble or prior to step b), the phrase --wherein the device comprises a

lysis reactor, a neutralizing reactor and a clarification reactor fluidly connected to one another by a tubing system and wherein transportation between the reactors is mediated by pressure or pumps--, the components of the device as is reference to flow rates are clarified. In step a) the recitation ''cultivating host cells in a fermentation broth-- provides clearer antecedent basis to reference to a fermentation broth. In steps b) and c) recitation of --transporting the lysed solution into the neutralizing reactor wherein the lysed cell solution is mixed with a neutralization solution to produce a mixture comprising a lysate and precipitate comprising cellular debris and impurities and wherein the lysate contain the biomolecules of interest-- corrects all of the deficiencies cited above. Similarly in d) amendment to --transporting the mixture into the clarification wherein the clarification reactor contains a retention layer that functions to retain the precipitate but the lysate flow from the clarification reactor. It is noted that reference thereafter to the lysis reactor, neutralizing reactor and clarification reactor should be preceded by the article --the--. As well, the phrases in steps b), c) and d) regarding "reactor is fluidly connected "can be deleted.

In claim 4, the claim should be amended to recite; --the particulate material consists of glass beads-- for clearer antecedent basis.

Appropriate correction is required.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 2, 3, 5, 9, 11-20, 23, 24, 40, 41 and 44 are rejected under 35 U.S.C. 102(e) as being anticipated by Nochumson (US 20060106208; see entire document). **This rejection is maintained for reasons of record in the office action mailed 4/30/08. Newly added claims 43 and 44 have been added to the rejection.**

Nochumson et al teach methods of purification of biomolecules using automated and semi-automated continuous units, which given the broadest interpretation can be considered reactors as the described reactions are undertaken in these units. As demonstrated in figure 2 and described in ¶ 0041, the cell suspension is loaded and undergoes alkaline lysis following which neutralization occurs. Following this, the lysate is clarified from precipitated cellular debris and impurities (RNA, chromosomal DNA, endotoxin, denatured plasmid). In these steps, the DNA flows through while the impurities remain in the column. The method is performed on a continuous, flow-through device (see e.g. 0019) in which resuspended cells, lysis solution and neutralization solutions are mixed using continuous flow, in line. Nochumson et al teach that lysis solution and cells can either be combined without further mixing prior to entering the lysis reactor (see e.g.0055) or else can be introduced into the lysis reactor and combined for example by use of an impeller mixer (see e.g. ¶ 0036). In the case that the two are part of two independent flows that are mixed in the lysis reactor, one of skill in the art would recognize that these flows would reasonable make a single flow to an inline static mixer by use of a T or Y shaped connector these being configurations that would lead to a single flow (see e.g. ¶ 0055 and figure 1). Effluent from the lysis reaction was directed to neutralization which Nochumson et al

teaches occurs by flowing lysate and neutralization solution through an inline state mixer in a continuous mode wherein a continuous flow indicates that flow is constant (see e.g. ¶ 0080).

The lysate is clarified and this is said to occur by a variety of techniques known to those of skill in the art (see e.g. ¶ 0072-0073 and 0063). This occurs through fluid connections between the units (see e.g. ¶ 0019-0021 and 0054). As well pumps are used to distribute the lysate and mixtures throughout the method. Claim 24 recites that the cells at step a) are cryo-pelleted. It is understood that this intends that the cells prior to use are cryo-pelleted. Nochumson et al teach that the cells can be frozen prior to use in the lysis reaction (see e.g. ¶ 0078) and in the broadest interpretation, these can be cryo-pelleted cells. Nochumson teaches that clarification occurs for example following alkaline lysis and neutralization by separation of the precipitated impurities by subsequent chromatographic steps (see e.g. ¶ 0048). The chromatographic step uses reactors comprising particulate material. Several wash steps are included as is clarification and concentration (see e.g. ¶ 0050-0053).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 2, 3, 5, 9, 12-20, 23, 24, 40 and 41 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nochumson (US 20060106208; see entire document) in view of Craig (U.S. Patent No. 6,381,967; see entire document). **This rejection is maintained for reasons of record**

in the office action mailed 4/30/08. Newly added claims 43 and 44 have been added to the rejection.

Applicants claim a method to purify a biomolecule of interest wherein a cell mass obtained by cultivating host cells to produce the biomolecule are cryo-pelleted.

The teachings of Nochumson et al are as above. While, Nochumson teaches that the cells are frozen, there are specific means of cryo-pelleting that Nochumson does not teach.

Craig teaches problems that cause cell death during cell freezing, including death due to formation of large sharp ice crystals, and also cell poisoning due to osmotic dehydration by formation of ice crystals. Craig teaches that freezing can involve a process of vitrification, which is the solidification of solutions at low temperature without ice crystal formation. Craig teaches that the higher the speed of the temperature change, the lower the viscosity required to vitrify and faster freezing rates lead to smaller ice crystals (see column 1, lines 16-44, for example). Craig teaches that the goal of any cryopreservation process is to minimize cell damage (see column 2, lines 1- 30, for example). Craig teaches a freezing method in which a liquid sample is transformed into small drops that are directly contacted with a partially solidified refrigerant. Craig teaches that this method is useful for substances that are susceptible to ice crystal or osmotic damage such as cells, plant material, tissue culture cells, sperm and embryos (see column 3, lines 20-25, column 4, lines 29-40, and column 12, lines 9- 20, see, for example).

It would have been obvious to the skilled artisan at the time the invention was made to use the rapid freezing method as taught by Craig to form bacterial cell cryo- pellets for storage prior to a method of biomolecule purification as rendered obvious by QIAGEN and Santoro et al because QIAGEN suggests that the harvested bacterial cells can be frozen before use and Craig

teaches an advantageous method of freezing cells. The motivation to freeze the bacterial cells by dropping them into partially solidified gas to form a cryopellet is the expected benefit of freezing the cells quickly in order to avoid formation of damaging and cytotoxic ice crystals as taught by Craig. There is a reasonable expectation of success to cryopellet bacterial cells before use since this has worked previously as taught by Craig. Given the teachings of the prior art and the level of skill of the ordinary skilled artisan at the time the invention was made, it must be considered that said ordinary skilled artisan would have had a reasonable expectation of success in practicing the claimed invention.

Claims 2-9, 11-20, 23, 24, 40, 41, 43 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nochumson (US 20060106208; see entire document) in view of Marquet et al (U.S. 5,561,064; see entire document) or Gonzalez et al (U.S. 5,783,686; see entire document). **This rejection is maintained for reasons of record in the office action mailed 4/30/08. Newly added claims 43 and 44 have been added to the rejection.**

Applicants claim a method to purify a biomolecule of interest wherein a cell mass obtained by cultivating host cells to produce the biomolecule are clarified using glass beads or sinter plates.

The teachings of Nochumson et al are as above. While, Nochumson et al teach that lysates produced by alkaline lysis and neutralization are also clarified, Nochumson et al do not teach that the filtrations utilize glass beads or sinter plates.

The art is replete with methods for clarification of plasmid DNA as well as other biomolecules in which lysates are clarified from impurities are filtered through sinter plates or

glass beads. Gonzalez et al teach that purification systems rely upon the ability of DNA to bind glass beads. Marquet et al teach advances in filtration devices for purification of biomolecules. The filtration devices are scalable, remove contaminants, and do not rely upon addition of extraneous proteins such as RNAse, organic extractants or mutagenic reagents (see e.g. bridging ¶ col 2-3). Marquet et al teach that cell debris and impurities can be removed from the lysate containing DNA by filtration through a material that is porous enough for plasmid DNA to pass through, but not insoluble material. Marquet et al teach that the filter device can be comprised of a porous fritted glass disks (see e.g. col 8, line 23-50). This method requires application of pressure for example which requires that pressure be placed above the filter to force outflow of the lysate and functions as a distribution means to force the lysate to reach the retention layer.

As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Exparte Smith --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In this case, it would have been obvious to the skilled artisan at the time the invention was made to use the filter systems as taught by Gonzalez et al and Marquet et al in the methods of Nochumson et al because Gonzalez and Marquet et al teach that using glass discs as well as glass beads was well known in the art and could be used in scale up methods and because Nochumson et al teaches that a variety of methods for DNA clarification could be used in methods of large scale purification of DNA. As well, it is within the ordinary skill of the art to use available methodologies to purify DNA and one would have been motivated to do so in order as the ability to modify filtration systems by applying conventional methodologies was well known in the art. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art,

and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Claims 2-9, 11-20, 23, 24, 40-42 and 44 are rejected under 35 U.S.C. 103(a) as being unpatentable over Nochumson (US 20060106208; see entire document) in view of Demaggio et al (5,846,764; see entire document) or (Rudi et al (U.S. 6,617,105; see entire document). **This is a new rejection necessitated by applicants' amendment.**

Applicants claim a method to purify a biomolecule of interest wherein using a device comprising a lysis reactor wherein the lysis reactor comprises glass beads.

The teachings of Nochumson et al are as above. While Nochumson et al teach that lysates produced by alkaline lysis, Nochumson et al do not teach that the lysis reactor utilize glass beads.

Demaggio et al teach lysis in buffer further comprising glass beads (example 7). The glass beads are used to grind the cells to improve lysis (see e.g. Rudi et al, line 14-34).

As an initial point, KSR forecloses the argument that a specific teaching, suggestion or motivation is required to support a finding of obviousness. See the recent Board decision Exparte Smith --USPD2d--., slip op. at 20, (BD. Pat. App. & Interfer. June 25, 2007). In this case, it would have been obvious to the skilled artisan at the time the invention was made to use glass beads as taught by Rudi et al or Demaggio et al in the methods of Nochumson et al because Rudi et al or Demaggio et al teach that using glass beads was well known in the art and could be used to lyse cells and because Nochumson et al teaches a step of lysis in methods of purifying biomolecules from cells. As well, it is within the ordinary skill of the art to use available methodologies to lyse cells comprising a desired biomolecule and one would have been

motivated to do so in order as the ability to modify conventional methodologies with well known techniques. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Response to Argument

Applicants' arguments filed 9/2/08 have been fully considered but they are not persuasive. Applicants argue that the lysis reactor of Nochumson et al does not provide teachings of a lysis reactor with "a particulate material". However, neither the claims nor the specification attribute special meaning to the phrase "a particulate material". As such, the teachings of Nochumson encompass a lysis reactor comprising a particulate material. Consider for example ¶ 0019 "Surprisingly, be performing alkaline lysis using a high concentration of unbuffered salt, not only is denatured chromosomal DNA, protein, and cellular debris trapped in precipitable salt/detergent complex". Both a high concentration of buffered salt and a precipitate of salt and detergent are particulate materials. The next step is precipitation of these particulate materials, which occurs through neutralization (see e.g. ¶ 0092). The tubing will be expected to be absent evidence to the contrary, essentially filled with this precipitate.

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MARIA B. MARVICH whose telephone number is (571)272-0774. The examiner can normally be reached on M-F (7:00-4:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph Woitach, PhD can be reached on (571)-272-0739. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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